REMARKS

Claims 21-27 and 30-49 are pending in this application. Claims 27 and 30-32 are pending, claim 33 is allowed, claims 21-23 and 34-49 are withdrawn from consideration, and claims 28-29 are canceled.

The Examiner states that claims 24-32 are not enabled under 35 USC 112, first paragraph because the specification does not include information about the deposit of RAdEs at European Collection of Cell Cultures (ECACC). This is respectfully traversed.

Applicant's respectfully disagree that a deposit of RadEs is required in order to enable claims 24-32. Claim 24 has been amended to incorporate the subject matter of claim 21. A description of how to make the vaccine of claim 24 is found throughout the specification. For example, the Examiner's attention is drawn to pages 3 and 5 and Example 2 of the specification.

In addition attached is a copy of the notification from European Collection of Cell Cultures (ECACC) that RadEs has been accepted as a patent deposit, in accordance with The Budapest Treaty of 1977 on December 17, 2004.

Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 24-32 under 35 USC 112, first paragraph on the basis that the specification is not enabling for the recombinant adenovirus RadEs vaccine. This is respectfully traversed.

The Examiner states that claims are not enabling because the phrase "vaccine" implies protection from infection with a pathogen. Attached are definitions of vaccine from 1) Wikipedia, Medical Dictionary from The Free Dictionary and dictionary from Biology-Online.org that define a vaccine as "a biological preparation that improves immunity to a

particular disease" and that vaccines can be prophylactic or therapeutic. Therefore, as described in the specification, the vaccine of this invention improved immunity against JEV. The claims are enabled and it is respectfully requested that this rejection be withdrawn.

The Examiner rejects claims 24-32 under 35 USC 103(a) as being unpatentable over Kaur in view of Jaiswal. This is respectfully traversed.

The Examiner draws the conclusion that it would have been obvious to substitute one known element Dengue Virus Type 2 envelope protein for another JEV E secretory protein. Applicants maintain that the Examiner has not met the burden of "articulating reasoning with rationale underpinning to support the legal conclusion of obviousness". There is no disclosure in either of the cited references that envelope proteins of Dengue Virus Type 2 are substitutable for any secretory proteins of JEV and that a vaccine that includes these envelope proteins would be effective to improve immunity against JEV.

The key elements for the exemplary rationales are (a) whether there is a motivation (or reason) for combining or modifying a reference (with the TSM rationale) or (b) whether there is predictability or a reasonable expectation of success. The Examiner has not shown that there is a motivation or reason to combine these references, and based on the results described in the specification, the results obtained were not predictable.

Following KSR, the Federal Circuit may find a claim obvious if the prior art points in the general direction of the invention (thereby arguably making it obvious to try) and those skilled in the art would believe that what was pointed to by the prior art would have a reasonable expectation of success.

In this case, the cited references do not point in the general direction of a recombinant vaccine as claimed and, given the disclosure in the references , there is no reasonable expectation of success based on the cited references.

The Examiner's attention is drawn to pages 5 to 8 of the specification where it is disclosed that:

> Mice were immunized intra-muscular (IM) and orally with RAds. Oral route of virus delivery induced low titers of anti-JEV antibodies that had only little JEV neutralizing activity. IM immunizations with both RAdEa and RAdEs resulted in high titers of anti- JEV antibodies. Interestingly, RAdEa induced very low titers of JEV neutralizing antibodies whereas RAdEs inoculation resulted in high titers of JEV neutralizing antibodies. Splenocytes from mice immunized IM with RAds secreted large amounts of interferon-y and moderate amounts of interleukin-5. These splenocytes also showed cytotoxic activity against JEV-infected cells. Mice immunized IM with RAdEs showed complete protection against the lethal dose of JEV given intra-cerebral.

On page 20 of the specification it is stated:

> Challenge experiments indicated that mice immunized IM with the adenovirus synthesizing the membrane-anchored form of JEV E protein did not develop protective immunity whereas those immunized with recombinant synthesizing the secretory form of JEV E protein developed robust anti-JEV protective immunity resulting in 100% protection. These results show that RAd-based JEV immunizations are superior to naked DNA immunizations, which imparted only about 50-60% protection in a mouse challenge model (15). It is interesting that level of protection was similar (50-60%) when mice were immunized with plasmid DNA synthesizing Ea or Es proteins (15) whereas in the present work Es induced significantly superior protective immune response than the Ea protein. This may be related to a more efficient delivery of JEV transgene using RAd than the direct injection of naked plasmid DNA for immunization.
> Our finding is, however, consistent with reports from others where truncated form of JEV or Dengue E protein (leading to its secretion) was found to be more immunogenic than the membrane-anchored form of the E protein (14,37).
>
> Poor anti-JEV antibody induction by oral immunization with RAds was also reflected in poor cytokine secretion by splenocytes in presence of JEV. While very little IFN-y was secreted by splenocytes from mice immunized orally with RAdEs or RAdEa, significant amounts of IFN-y were secreted by splenocytes obtained from mice immunized IM with RAdEa or RAdEs. Splenocytes from IM immunized mice also synthesized moderate amounts of IL-5 that was not detectable in cultures of splenocytes obtained from mice immunized orally with RAds. Mice immunized IM with both RAdEa and RAdEs had significant CTL activity, which was undetectable in mice immunized orally with RAds or IM with the vaccine. Oral immunization with RAdEs at lower dose resulted in IgGl dominated immune responses; ratio of IgGl/IgG2a end- point titers was 6.5. This is consistent with studies on oral immunization of mice with RAd synthesizing rabies glycoprotein where abundance of anti rabies IgGl was recorded (46). The IM inoculation of RAdEa and RAdEs also resulted in preponderance of IgGl kind of antibodies. No data could be found in

literature on antibody isotypes when adenovirus recombinants are delivered IM. Our results indicating the preponderance of IgG1 type antibodies, secretion of IFN-γ and IL-5 by splenocytes and induction of CTLs suggest that IM inoculation of mice with RAds synthesizing JEV E protein activates both the humoral and the cellular arms of the immune system, and immune responses of both Th1 and Th2 type are induced.

The results presented in this invention show that RAd synthesizing the secretory form of JEV E protein imparted robust immunity in mice against lethal dose of JEV given intra-cerebral. This makes RAdEs a potential candidate vaccine against JEV. Further, safety profile of the vaccine of the instant application was studied. The vaccine is found to be safe for administration. None of the immunized mice showed any obvious complications.

Therefore, as there is no combination of the references that make the claims obvious, it is respectfully requested that the rejection be withdrawn.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested. If any fees are required, they may be charged to deposit account 12-0425.

Respectfully submitted,

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